DOI: 10.1111/dme.13858

Research: Epidemiology

Cardiovascular disease management in people with diabetes outside North America and Western Europe in 2006 and 2015

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Accepted 2 November 2018

Abstract

Aim Optimal treatment of cardiovascular disease is essential to decrease mortality among people with diabetes, but information is limited on how actual treatment relates to guidelines. We analysed changes in therapeutic approaches to anti-hypertensive and lipid-lowering medications in people with Type 2 diabetes from 2006 and 2015.

Methods Summary data from clinical services in seven countries outside North America and Western Europe were collected for 39 684 people. Each site summarized individual-level data from outpatient medical records for 2006 and 2015. Data included: demographic information, blood pressure (BP), total cholesterol levels and percentage of people taking statins, anti-hypertensive medication (angiotensin-converting enzyme inhibitors, calcium channel blockers, angiotensin II receptor blockers, thiazide diuretics) and antiplatelet drugs.

Results From 2006 to 2015, mean cholesterol levels decreased in six of eight sites (range: −0.5 to −0.2), whereas the proportion with BP levels > 140/90 mmHg increased in seven of eight sites. Decreases in cholesterol paralleled increases in statin use (range: 3.1 to 47.0 percentage points). Overall, utilization of anti-hypertensive medication did not change. However, there was an increase in the use of angiotensin II receptor blockers and a decrease in angiotensin-converting enzyme inhibitors. The percentage of individuals receiving calcium channel blockers and aspirin remained unchanged.

Conclusions Our findings indicate that control of cholesterol levels improved and coincided with increased use of statins. The percentage of people with BP > 140/90 mmHg was higher in 2015 than in 2006. Hypertension treatment shifted from using angiotensin-converting enzyme inhibitors to angiotensin II receptor blockers. Despite the potentially greater tolerability of angiotensin II receptor blockers, there was no associated improvement in BP levels.

Diabet. Med. 36: 878–887 (2019)

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Introduction

Cardiovascular disease (CVD) is the leading cause of mortality and morbidity among people with diabetes, and is the main contributor to health costs related to diabetes [1,2]. Numerous randomized clinical trials have

What's new?

- Mean total cholesterol levels in people with diabetes decreased with a simultaneous increase in statin use.
- The percentage of people with blood pressure (BP) > 140/90 mmHg increased, which may reflect the change in BP targets from ≤ 130/80 to ≤ 140/90 mmHg that occurred between 2006 and 2015.
- Anti-hypertensive treatment approaches shifted towards using more angiotensin II receptor blockers with a simultaneous decline in the use of angiotensin-converting enzyme inhibitors.
- Although improved control of high cholesterol in people with diabetes was encouraging, further efforts are required to improve hypertension management in people with diabetes.

demonstrated the benefits of blood pressure (BP) and dyslipidaemia treatment in preventing or delaying the complications of diabetes, including CVD. Management of CVD has therefore been emphasized as an indispensable part of diabetes treatment by most guidelines [1–7].

There are several reports on cardiovascular risk management in people with diabetes from North America and Western Europe [8,9]. The National Health and Nutrition Examination Surveys (NHANES) demonstrated a decline in the prevalence of hypertension from 64% to 37%, and in the prevalence of high cholesterol levels from 72% to 55% among adults with diabetes in the USA between 1971 and 2000 [8]. The Health Survey for England (HSE) reported a linear decline in cholesterol levels parallel to an increase in the proportion of people with diabetes on lipid-lowering drugs (2.2% to 47.4%) between 1994 and 2009 [9]. The HSE also reported a significant decline in both systolic (SBP) and diastolic blood pressure and an increase in the use of anti-hypertensive drugs [9].

There is limited information about how hypertension and dyslipidaemia treatments are actually delivered outside North American and Western Europe. These data are important because they show how targets translate into practice, and how changes in treatment approaches and targets are reflected in actual practice. Such information will also provide a basis for establishing interventions to improve the delivery of diabetes care with a focus on reducing the risk of CVD in people with diabetes.

Obtaining data on treatment approaches in diabetes requires access to medical records. However, only electronic medical records have the potential to allow extraction of the large amounts of objective data that are needed for such projects. The availability of such electronic databases has facilitated reports on diabetes management in North America and Western Europe. In recent years, use of such record systems has spread to other parts of the world, allowing for the development of projects to examine/investigate how people with diabetes are actually managed, including the Real World Experience (RWE) project described here.

The RWE project identified a series of data sources around the world, outside North America and Western Europe. These electronic data sources captured individual-level information from all people with diabetes attending specific clinical services.

Given that there is not enough information on the treatment of dyslipidaemia and hypertension outside North America and Western Europe, the aim of this study was to explore changes in anti-hypertensive, lipid-lowering and antiplatelet medications, as well as in BP and cholesterol target achievement in people with diabetes from 2006 and 2015, outside North America and Western Europe.

Methods

Through a series of meetings and personal links, we sought to identify clinical services outside North America and Western Europe that were able to produce clinic- or population-wide reports on the provision of care to people with diabetes. We identified eight data sources from seven countries (Argentina, Australia, Hong Kong, India, Japan, Saudi Arabia and South Africa) that captured individual-level information from all people with Type 2 diabetes within a given service or jurisdiction. This is a retrospective study, in which we extracted and summarized data from all individuals with diabetes aged > 18 years attending each of the eight clinical services.

There were seven specialist care services and one primary care/specialist care data source. Each site extracted and summarized data from the medical records of all those attending outpatients in the years 2006 and 2015, using a standardized data-reporting form developed for this project to collect and report data. Data included demographics, disease history, diabetic complications, BP, cholesterol levels, and anti-hypertensive, lipid-lowering and antiplatelet medications. For people who had more than one laboratory result or measurement during the year, the result closest to the middle of the year (30 June) was chosen. If there were two results with the same date, an average was taken. If there were two or more results with different dates equidistant to the middle of the year, the value was chosen depending on the quarter in which it fell, in the order: second, third, fourth or first quarter.

The percentage of people who reached BP targets of ≤ 140/90 and ≤ 130/80 mmHg, and the percentage of people on anti-hypertensive therapy were reported by each site. Hypertension was defined as BP > 140/90 mmHg or taking anti-hypertensive medications. To understand how well people with hypertension were managed, the percentage of those with BP above target and who were not on anti-hypertensive medications was also reported. Information was also collected separately for proportions of each class of anti-

Table 1 Characteristics of people with Type 2 diabetes in 2006 and 2015 stratified by clinical service

Country (centre)	Year	N	Male*	Age (years)	HbA_{1c} mmol/mol	HbA_{1c} %	BMI (kg/m^2)	Duration of diabetes (years)
Argentina (Centro de Endocrinología Experimental y Aplicada)								
	2006	2 146	48.4 (1039)	58.1 (11.1)	61	7.7 (1.8)	30.1 (5.4)	9.3 (9.0)
	2015	1 828	49.6 (907)	54.7 (9.9)	63	7.9 (2.1)	32.1 (6.4)	8.9 (7.2)
P-value				< 0.001	< 0.001		< 0.001	0.06
Australia (Baker Heart and Diabetes Institute, Melbourne)								
	2006	4 080	57.2 (2331)	61.7 (15.6)	60	7.6 (1.4)	29.8 (6.0)	9.8 (9.8)
	2015	4 059	60.6 (2459)	61.8 (15.7)	61	7.7 (1.4)	29.7 (5.8)	13.8 (10.4)
P-value				0.38	< 0.001		0.22	P< 0.001
Australia (Royal Prince Alfred Hospital, Sydney)								
	2006	1 406	58.2 (818)	60.3 (13.6)	58	7.5 (1.5)	30.7 (6.3)	11.2 (8.4)
	2015	1 351	59.5 (804)	59.6 (15.3)	64	8.0 (1.7)	30.2 (6.4)	14.2 (10.2)
P-value				0.1	< 0.001		0.01	P< 0.001
Hong Kong (Prince of Wales Hospital)								
	2006	788	49.2 (388)	58.5 (12.9)	57	7.4 (1.6)	25.7 (4.3)	6.6 (7.1)
	2015	2 043	54.2 (1108)	59.9 (12.0)	60	7.6 (1.4)	26.2 (4.8)	11.3 (8.8)
P-value				0.003	< 0.001		0.005	P< 0.001
India (Dr. A Ramachandran's Diabetes Hospitals)								
	2006	6 022	58.4 (3516)	58.0 (12.0)	88	8.4 (1.8)	26.9 (4.5)	13.7 (9.3)
	2015	13 348	59.5 (7945)	54.0 (13.0)	85	8.1 (1.7)	27.5 (4.8)	11.5 (9.3)
P-value				< 0.001	< 0.001		P< 0.001	P< 0.001
Japan (Shiga University of Medical Science)								
	2006	384	53.9 (207)	63.0 (11.0)	61	7.7 (1.1)	24.0 (3.8)	18.0 (10.0)
	2015	291	59.8 (174)	73.0 (5.0)	55	7.2 (1.0)	23.5 (3.5)	17.0 (11.0)
P-value				< 0.001	< 0.001		0.04	0.1
Saudi Arabia (Diabetes Center at AlNoor Specialist Hospital)								
	2006	383	41.5 (159)	53.5 (16.8)	60	7.6 (2.1)	31.3 (5.6)	8.9 (7.7)
	2015	276	51.4 (142)	56.4 (12.1)	68	8.4 (1.8)	31.7 (6.7)	9.6 (8.8)
P-value				0.007	< 0.001		0.202	0.139
South Africa (Inkosi Albert Luthuli Central Hospital)								
	2006	601	34.6 (208)	49.3 (17.5)	83	9.7 (2.5)	30.2 (7.3)	13.2 (11.0)
	2015	681	36.4 (248)	46.5 (20.4)	75	9.0 (2.3)	29.9 (7.5)	14.0 (10.3)
P-value				0.004	< 0.001		0.23	0.08

Values are given as mean (SD) except * *n* (%).
P-values were calculated using the Student's *t*-test for means and *z*-test for proportions comparing the values in 2006 and 2015.

hypertensive medication including angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), thiazide diuretics and calcium channel blockers. The proportions of people using statins and antiplatelet medications were also reported by each site.

Analyses were conducted using Stata (v. 14; Stata Corp, College Station, TX, USA). We reported continuous variables as mean ± standard deviation (SD) and categorical variables as proportions. Differences in the general characteristics of the study population between 2006 and 2015, were assessed using the Student's *t*-test for means and the *z*-test for proportions, as appropriate. For all analyses, a *P*-value < 0.05 was considered statistically significant.

Because this was an analysis of data already collected for clinical purposes, and no individual-level data left any clinical sites, no consent was obtained from the study population, and some sites did not require local ethics approval. The study was approved by the Monash University Human Research Ethics Committee (number 1441), and the Alfred Ethics Committee (number 64/15) in Australia and in some of the sites, as required by local guidelines.

Results

Study population

For the purpose of this analysis, the RWE study includes 39 684 people with diabetes from eight clinical sites in seven different countries (Table 1). All those in the study population received specialist care services, except in Argentina where 26% and 74% were treated in primary care in 2006 and 2015, respectively. There was heterogeneity in the characteristics of the study population between sites. Sample size varied from 291 in Japan to 13 348 in India. The mean age of the population with diabetes ranged from 46 to 73 years. Table 2 shows that from 2006 to 2015, the mean age of the population decreased significantly in Argentina, India and South Africa, increased significantly in Hong Kong, Saudi Arabia and Japan, and remained unchanged in Australia. BMI increased significantly by 1 kg/m^2 in Argentina and by 0.5 kg/m^2 in India, and decreased significantly by 0.5 kg/m^2 in Australia (Sydney), Hong Kong and Japan. The change in mean BMI was not significant at other sites.

Table 2 Hypertension and dyslipidaemia management in people with Type 2 diabetes in 2006 and 2015 stratified by clinical service

							Prevalence of abnormal blood pressure (mmHg)*					
			Cholesterol (mmol/l)		Blood pressure (mmHg)		Above target		Hypertension†		Untreated hypertension‡	
Country (centre)	Year	*N*	Population statins	Total population	Systolic	Diastolic	> 130/80	> 140/90	> 130/80	> 140/90	> 130/80	> 140/90
Argentina												
	2006	2 146	5.2 (1.1)	5.5 (1.1)	132.4 (15.9)	80.1 (9.7)	22.8	5.2	68.4	65.5	11.5	10.7
	2015	1 828	4.9 (1.1)	5.1 (1.1)	128.9 (16.3)	78.2 (11.0)	17.6	6.9	63.3	61.1	17.6	13.0
P-value			< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	0.13	< 0.001	0.004	< 0.001	0.01
Australia (Melbourne)												
	2006	4 080	4.3 (1.1)	4.1 (1.1)	129.8 (16.7)	74.1 (9.2)	40.1	18.9	75.0	70.8	18.1	12.0
	2015	4 059	4.4 (1.7)	4.2 (1.7)	133.5 (17.2)	75.5 (11.2)	63.1	33.5	77.9	68.1	31.2	24.3
P-value			< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	0.01	0.02	< 0.001	< 0.001
Australia (Sydney)												
	2006	1 406	4.5 (1.1)	4.3 (1.1)	130 (17.0)	74.0 (10.0)	49.3	23.6	83.4	77.3	18.3	12.7
	2015	1 351	4.3 (1.9)	4.1 (1.9)	123 (15.1)	70.7 (9.3)	26.0	9.8	70.2	66.0	16.9	10.7
P-value			< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	0.22	0.051
Hong Kong												
	2006	788	4.8 (1.1)	4.4 (1.1)	130.6 (19.9)	73.6 (10.9)	51.9	29.1	74.0	64.1	31.1	21.4
	2015	2 043	4.3 (0.9)	4.1 (0.9)	133.6 (18.7)	73.7 (11.5)	57.3	32.3	78.8	71.8	28.8	26.9
P-value			< 0.001	< 0.001	< 0.001	0.41	< 0.001	0.06	0.01	< 0.001	0.06	0.001
India												
	2006	6 022	4.4 (1.0)	4.4 (1.0)	132.0 (15.0)	81.0 (6.0)	62.3	12.8	62.3	12.8	48.7	38.5
	2015	13 348	4.2 (1.2)	4.2 (1.1)	130.0 (17.0)	81.0 (8.0)	52.8	15.8	52.8	15.8	45.9	35.7
P-value			< 0.001	< 0.001	< 0.001	0.50	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001
Japan												
	2006	384	5.1 (0.8)	5.1 (0.8)	132.0 (16.0)	72.0 (10.0)	57.3	28.9	75.0	65.9	32.0	33.3
	2015	291	4.8 (0.8)	4.6 (0.9)	140.0 (16.0)	76.0 (12.0)	74.5	50.2	87.6	77.7	42.0	36.3
P-value			< 0.001	0.423	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	0.003	0.21
Saudi Arabia												
	2006	383	5.0 (1.3)	5.2 (1.6)	127.3 (79.3)	79.3 (8.7)	30.8	13.6	50.4	43.3	26.3	7.7
	2015	276	4.7 (1.2)	4.7 (1.3)	134.5 (63.4)	76.7 (7.8)	42.3	20.6	65.2	52.5	39.2	24.6
P-value			0.001	< 0.001	0.10	< 0.001	0.001	0.008	< 0.001	0.01	0.0002	< 0.001
South Africa												
	2006	601	4.9 (1.2)	5.1 (1.2)	133.4 (19.9)	76.1 (10.2)	52.7	31.0	80.0	75.0	11.6	4.3
	2015	681	4.4 (1.2)	4.4 (1.2)	131.0 (16.0)	74.0 (11.0)	55.5	48.0	95.5	79.4	28.3	17.5
P-value			< 0.001	< 0.001	0.01	< 0.001	0.14	< 0.001	< 0.001	0.04	< 0.001	< 0.001

Values are presented as mean (SD) except *percentage.
†Percentage of those with blood pressure above target or on anti-hypertensive medications. ‡Percentage of those with blood pressure above target who were not on anti-hypertensive medications.
P-values calculated were using the Student's *t*-test for means and *z*-test for proportions comparing values in 2006 and 2015.

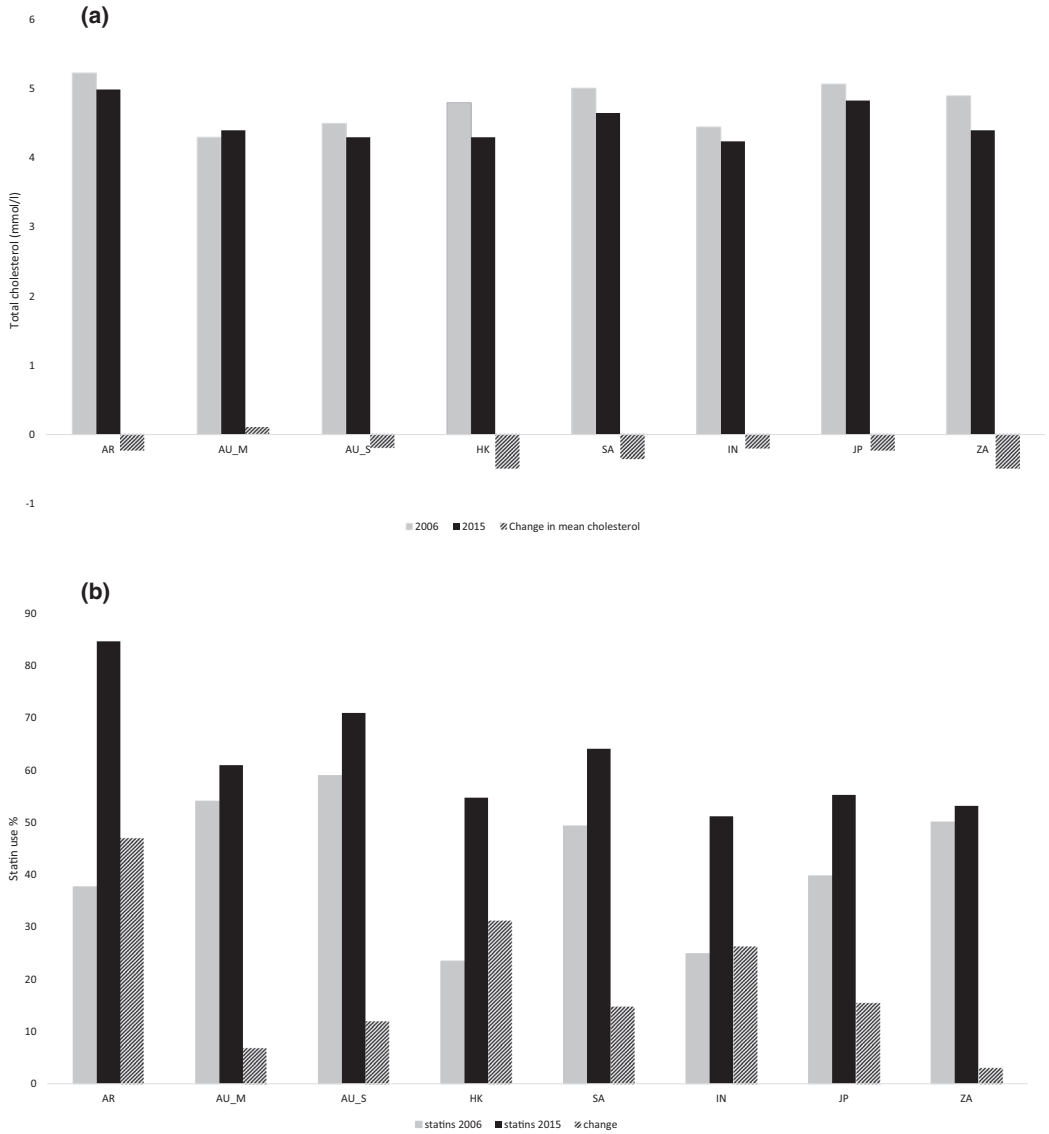

FIGURE 1 (a) Mean total cholesterol in 2006 and 2015, and change (mmol/l) from 2006 to 2015. (b) Prevalence of statin use in 2006 and 2015, and percentage point change from 2006 to 2015. AR, Argentina; AU_M, Australia, Melbourne; AU_S, Australia, Sydney; HK, Hong Kong; SA, Saudi Arabia; IN, India; JP, Japan; ZA, South Africa

Duration of diabetes decreased significantly in India, increased in Australia and Hong Kong, and remained unchanged at other sites. Mean HbA_{1c} increased significantly in Argentina (by 0.2 percentage points), Australia (Melbourne) (0.1 percentage points) Australia (Sydney) (0.5 percentage points), Hong Kong (0.2 percentage points) and Saudi Arabia (0.8 percentage points), and decreased significantly in Japan (0.5 percentage points) and South Africa (0.7 percentage points).

Management of dyslipidaemia

There was a decline in mean cholesterol level among people with diabetes in seven of the eight clinical sites (range: −0.5 to −0.2 mmol/mol) and an increase in Australia (Melbourne), from 2006 to 2015 (Fig. 1a). This improvement was accompanied by a large increase in statin use during the study period (range: 3.1 to 47 percentage points) (Fig. 1b). However, the magnitude of the reduction in mean cholesterol levels differed by site (Fig. 1a). Argentina, Japan, Saudi Arabia and South Africa showed the highest proportion of people with high cholesterol in 2006 and 2015. The greatest reductions in mean cholesterol levels were observed mainly at those sites with the highest mean cholesterol levels in 2006 (Argentina, Hong Kong, Japan, Saudi Arabia and South Africa). At each site, at least half of the population with diabetes was on statin therapy in 2015 (Table 2).

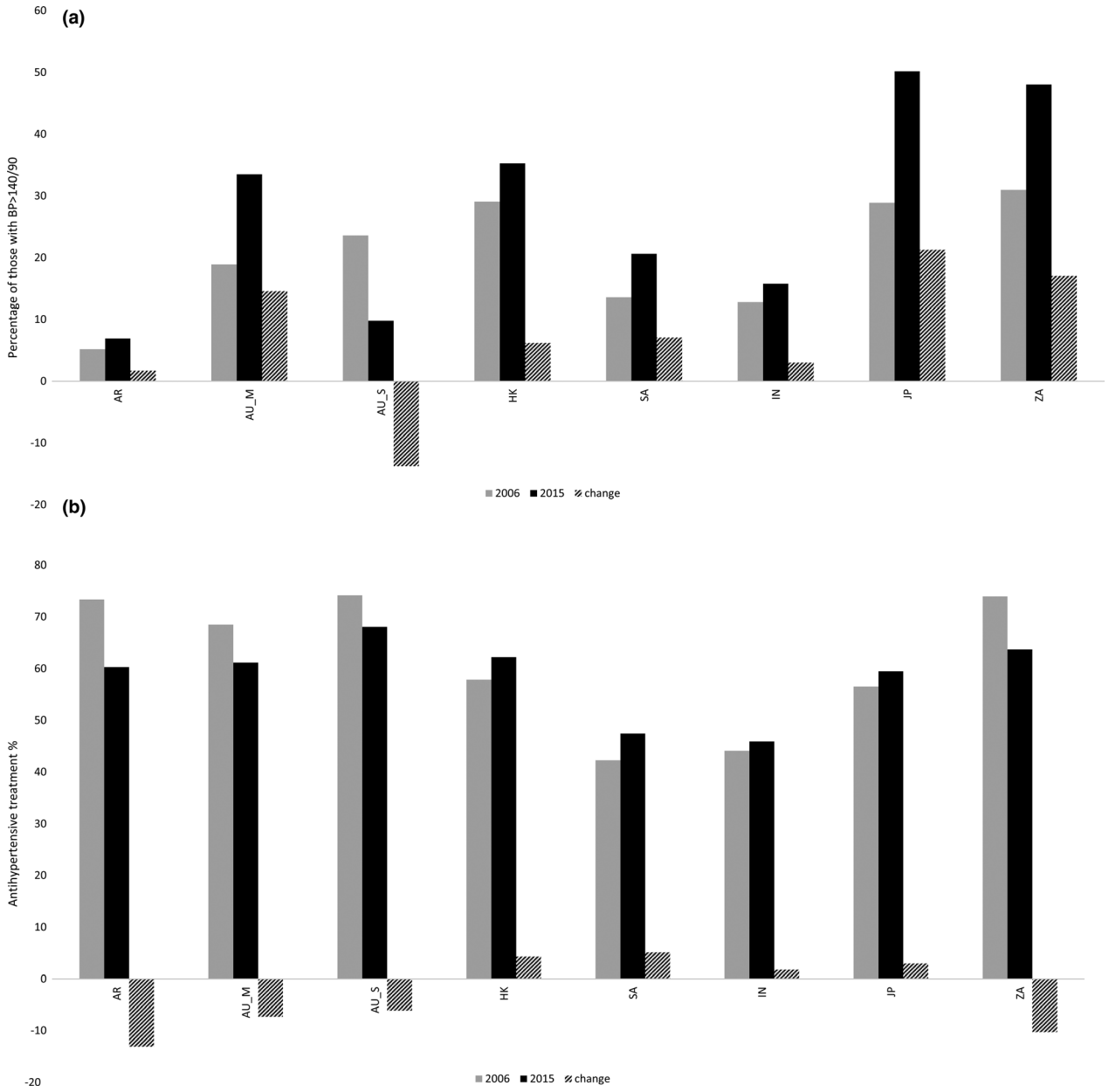

FIGURE 2 (a) Prevalence of patients with BP>140/90 in 2006 and 2015, and percentage point change from 2006 to 2015. (b) Prevalence of antihypertensive medications use in 2006 and 2015, and percentage point change from 2006 to 2015. AH, anti-hypertensive medications; AR, Argentina; AU_M, Australia, Melbourne; AU_S, Australia, Sydney; HK, Hong Kong; SA, Saudi Arabia; IN, India; JP, Japan; ZA, South Africa

Management of hypertension

In 2015, South Africa and Japan had the highest prevalence of hypertension, defined as BP ≥ 140/90 mmHg or taking anti-hypertensive medication (Table 2). There was an increase in the proportion of people with BP ≥ 140/90 mmHg (1.4–21.3 percentage points) at all sites except Australia (Sydney) where there was a 13.8 percentage point reduction in people with BP > 140/90 mmHg (Fig. 2a). The prevalence of anti-hypertensive medication use declined significantly in Argentina, Australia and South Africa (range: −13.1 to −7.3 percentage points), increased significantly in Hong Kong and India (range 1.8 to 4.3 percentage points), and remained unchanged in Japan and Saudi Arabia.

Table 2 shows that SBP decreased significantly in Argentina (from 132 to 129 mmHg), Australia (Sydney) (130 to 123 mmHg) and India (132 to 130 mmHg). Mean SBP increased in Australia (Melbourne) (130 to 133 mmHg), Japan (132 to 140 mmHg) and Saudi Arabia (127 to

Table 3 Prevalence of use of cardiovascular disease drug classes in people with diabetes in 2006 and in 2015 stratified by site

Country	Year	*N*	ARB	ACEi	Thiazides	CCB	Statins	Anti-platelet
Argentina								
	2006	2 146	8.9 (190)	52.4 (1124)	14.4 (310)	11.7 (252)	30.9 (664)	–
	2015	1 828	17.3 (317)	60.7 (1109)	16.1 (295)	12.7 (232)	52.0 (951)	35.9 (656)
P-value			< 0.001	< 0.001	0.08	0.16	< 0.001	N/A
Australia (Melbourne)								
	2006	4 080	35.0 (1429)	33.9 (1383)	26.0 (1061)	26.0 (1059)	54.1 (2207)	21.0 (857)
	2015	4 059	33.7 (1370)	22.0 (382)	25.7 (1042)	23.1 (937)	61.0 (2477)	30.7 (1247)
P-value			0.11	< 0.001	0.37	< 0.001	< 0.001	< 0.001
Australia (Sydney)								
	2006	1 406	32.9 (452)	37.9 (522)	16.3 (227)	21.6 (297)	59.0 (153)	38.5 (529)
	2015	1 351	38.7 (489)	25.1 (318)	N/A	26.1 (330)	71.0 (161)	31.0 (396)
P-value			< 0.001	< 0.001	N/A	0.002	< 0.001	< 0.001
Hong Kong								
	2006	788	5.1 (40)	35.2 (277)	N/A	29.7 (234)	23.5 (185)	19.0 (150)
	2015	2 043	18.4 (377)	30.8 (629)	3.1 (8.3)	35.4 (724)	54.8 (1119)	23.2 (474)
P-value			< 0.001	0.01	N/A	0.002	< 0.001	0.007
India								
	2006	6 022	19.6 (1077)	4.7 (258)	9.0 (439)	16.8 (925)	24.9 (1371)	18.1 (996)
	2015	13 348	27.3 (3649)	3.2 (426)	9.4 (1248)	15.6 (2081)	51.2 (6831)	21.4 (2862)
P-value			< 0.001	< 0.001	0.19	0.02	< 0.001	0.09
Japan								
	2006	384	27.3 (105)	18.8 (72)	14.8 (57)	29.7 (114)	39.8 (153)	33.6 (129)
	2015	291	45.0 (131)	7.9 (23)	17.5 (51)	32.6 (95)	55.3 (161)	28.9 (84)
P-value			< 0.001	< 0.001	0.17	0.21	< 0.001	0.09
Saudi Arabia								
	2006	383	5.2 (20)	30.3 (116)	9.4 (36)	14.6 (56)	49.3 (189)	70.8 (271)
	2015	276	20.3 (56)	24.6 (68)	8.3 (23)	18.5 (51)	64.1 (177)	59.1 (163)
P-value			< 0.001	0.053	0.31	0.09	< 0.001	< 0.001
South Africa								
	2006	601	4.0 (24)	56.1 (337)	36.4 (219)	47.6 (286)	50.1 (301)	49.1 (295)
	2015	681	14.2 (97)	42.3 (288)	22.6 (154)	33.8 (230)	53.2 (362)	37.3 (254)
P-value			< 0.001	< 0.001	< 0.001	< 0.001	0.14	< 0.001

Values are presented as *n* or *n* (%).
N/A, not available; ARB, angiotensin II receptor blocker; ACE, angiotensin-converting enzyme inhibitor; CCB, calcium channel blocker.
P-values were calculated using the *z*-test for proportions.

134 mmHg), whereas in other clinics, there was no significant change in mean SBP.

From 2006 to 2015, the prevalence of hypertension, defined as either anti-hypertensive medication use or a BP > 140/90 mmHg, decreased significantly in Australia (Sydney) (−11.3 percentage points), Australia (Melbourne) (−2.7 percentage points) and Argentina (−4.4 percentage points), and increased significantly at the other sites (range 3.0 to 11.8 percentage points). The prevalence of untreated hypertension increased significantly in Argentina (2.3 percentage points), Australia (Melbourne) (12.3 percentage points), Hong Kong (5.5 percentage points), Japan (3 percentage points), Saudi Arabia (16.9 percentage points) and South Africa (13.2 percentage points), and decreased significantly in Australia (Sydney) (2 percentage points) and India (2.8 percentage points). The proportion of people using each class of anti-hypertensive medication is presented in Table 3. ACE inhibitors were the most commonly prescribed anti-hypertensive medication in most sites, followed by calcium channel blockers and ARBs. Although there was no increase in the total proportion of people on anti-hypertensive treatment, there was a change in the type of medication used. There was a reduction in the proportion of people taking ACE inhibitors from 2006 to 2015. Simultaneously, utilization of ARBs increased. Furthermore, we observed huge variability in the use of ARBs and ACE inhibitors between sites. For example, the prescription of ARBs among people with diabetes varied from 4.0% in South Africa to 35.0% in Australia (Melbourne) in 2006; this heterogeneity in ARB usage persisted in 2015, when 14.2% and 45.0% used ARBs in South Africa and Japan, respectively. Of note, heterogeneity in the use of ACE inhibitors persisted from 2006 (from 4.7% in India to 56.1% in South Africa) to 2015 (from 3.2% in India to 60.7% in Argentina). For other types of medication, such as statin and antiplatelet agents, we did not observe such heterogeneity in the prescription rates between sites.

There was a mixed pattern for use of other anti-hypertensive medications such as thiazide diuretics and calcium channel blockers in different sites. Between 2006 and 2015, the prescription of thiazide diuretics decreased significantly in South Africa but did not change in other clinical sites. Utilization of calcium channel blockers decreased significantly in Australia (Melbourne), India and South Africa, increased significantly in Australia (Sydney) and Hong Kong, and remain unchanged in other sites. Prescription of aspirin and other

antiplatelet medications: decreased significantly in three sites, Australia (Sydney), Saudi Arabia and South Africa (range −11.8 to −7.5 percentage points); increased in Australia (Melbourne) (9.7 percentage points), Hong Kong (4.2 percentage points) and India (3.3 percentage points); and remained unchanged at other clinical sites (Table 3).

Discussion

This study provides information on CVD management in 39 684 people with Type 2 diabetes from seven countries. Despite the existence of heterogeneity between countries in terms of cardiovascular risk management, similar changes in treatment approaches can be observed. In general, mean cholesterol levels decreased in the study population in line with increased statin use. In addition, lower cholesterol levels among those on statins likely reflects the use of higher doses and more potent statins. The proportion of people on anti-hypertensive medication decreased slightly or remained unchanged with concomitant increases in the proportion of people with BP > 140/90 mmHg in most sites. Anti-hypertensive treatment patterns shifted from using predominantly ACE inhibitors towards using more ARBs. Nevertheless, the change to newer hypertension drugs was not associated with improvement in BP levels.

The benefit of statin use both for primary and secondary prevention of CVD events in people with diabetes is well-established and extensively investigated [10]. The American Diabetes Association (ADA) guidelines recommend a lower LDL-cholesterol target (< 1.8 mmol/l) for people with diabetes and a concomitant cardiovascular event than for the general population (< 2.6 mmo/l) [11]. The results of our study are consistent with those reported by the HSE, which showed that from 1994 to 2009, total cholesterol levels declined in people with diabetes from 6.1 to 4.5 mmol/l, in parallel with an increase in the prescription of statins from 2.2% to 47.4% [9]. A study of people with diabetes from Taiwan also showed a threefold increase in statin use in a 7-year period [12]. Similar to our findings, a study of people with Type 2 diabetes in the USA showed a substantial increase in statin use (from 4.2% in 1988 to 51.4% in 2010), accompanied by substantial improvement in the percentage of people achieving the LDL-cholesterol target of < 2.6 mmol/l from 9.9% to 56.2% [13].

Our study shows that nearly 80% of those with BP > 140/90 mmHg were taking anti-hypertensive medication. Reasons for failing to achieve the BP target despite receiving treatment for hypertension may include poor adherence [14,15], inadequate efficacy of anti-hypertensive medications, side effects of drugs and variability in BP measurement. BP management in hypertensive individuals with diabetes has undergone some significant changes over the past decade. ADA targets for management of hypertension among people with Type 2 diabetes have changed over time. In 2006, ADA guidelines recommended a BP target of 130/80 mmHg for people with diabetes. This was based on several large studies such as the Hypertension Optimal Treatment study and the United Kingdom Prospective Diabetes Study, which showed that maintaining BP levels < 130/80 mmHg reduced cardiovascular events in people with diabetes. However, the pooled analysis of mortality risk associated with the use of intensive BP targets vs. standard targets in people with Type 2 diabetes reported no benefit or even harm when the lower BP targets were achieved [16]. This meta-analysis demonstrated that although the use of intensive vs. standard BP targets might cause a small reduction in the risk for stroke, there was no evidence of benefit from intensive targets in reducing risk of mortality or myocardial infarction, but rather there was an increased risk of hypotension and other adverse events [16]. Thus, there has been a modification to recent guidelines recommending a less stringent BP target, i.e. 140/90 mmHg, with an emphasis on the individualization of BP management with regard to age and the existence of other risk factors. Another explanation for the lack of improvement in BP control is the variability in BP targets suggested by different guidelines. ADA guidelines recommend a BP target of < 140/90 mmHg [17] for people with diabetes, whereas the American Association of Clinical Endocrinologists/American College of Endocrinology AACE/ACE [4] and IDF [1] recommended a BP target of < 130/80 mmHg. In 2015, national guidelines for Australia and Japan also recommended a BP target of < 130/80 mmHg [18,19]. Despite the only change in target BP being a move away from 130/80 mmHg, it is concerning that the percentage of people with BP > 140/90 mmHg increased at all but one site. This suggests that raising BP targets from 130/80 to 140/90 mmHg can have the undesired effect of increasing the number of people failing to achieve the 140/90 mmHg target, and this should be considered in future guideline deliberations.

In this study, ACE inhibitors were the most popular anti-hypertensive medication at most sites, which is consistent with most guidelines. Nevertheless, we observed a shift from prescription of ACE inhibitors to ARBs from 2006 to 2015. According to guidelines [20,21], ACE inhibitors and ARBs (if intolerant to ACE inhibitors) are the first line of anti-hypertensive medication for people with diabetes. Calcium channel blockers, thiazides and thiazide-like diuretics are recommended as the second line of treatment when patients fail to reach the target with first-line drugs. Meta-analyses directly comparing ACE inhibitors and ARBs found that both had similar effects in reducing mortality and cardiovascular events [22]. However, ARBs have a better side effect profile than ACE inhibitors in regard to cough, which is reported in 44% in those on ACE inhibitors compared with only 4% for those on ARBs [23].

One of the reasons for the heterogeneity in prescribing anti-hypertensive medications between sites is the number of different classes of anti-hypertensive medications available.

Thus, health professionals have a range to choose from and choice is based on the availability, cost, side effects, tolerability and local guidelines.

The ADA recommended low-dose aspirin for secondary prevention of cerebrovascular and cardiovascular events [24], and for primary prevention for those with high risk of CVD. The high-risk group includes men and women with diabetes aged ≥ 50 years who have at least one additional major risk factor (family history of premature atherosclerotic CVD, hypertension, dyslipidaemia, smoking or albuminuria) and are not at increased risk of bleeding. In our study, use of antiplatelet therapy was generally below 50% and the change between 2006 and 2015 was variable. A recent population-based study in the USA showed a slight decrease in the prevalence of aspirin use for both primary and secondary CVD prevention from 2012 to 2015 [25]. Potential reasons for the variability in aspirin use in our study include controversy in recent years regarding the benefit of aspirin use among those without prior CVD events. Two studies published in 2008 and 2009, showed no clear benefit of aspirin use in the primary prevention of CVD events in people with diabetes. Furthermore, the Antithrombotic Trialists' (ATT) collaborators, in an individual patient-level meta-analysis in 2009, showed some evidence of sex disparity in that aspirin significantly reduced stroke only in women; by contrast, aspirin reduced the risk of atherosclerotic CVD only in men [26].

The strengths of our study include the large sample size and the non-trial setting that the data represent. Clinical trials are conducted under strict conditions that do not necessarily represent real-world situations in which people with diabetes are managed less rigorously. Although individual services are not necessarily representative of the population within which they are located, they provide information on all attending individuals, thus removing volunteer bias. Using data from medical records, our study observed management in real-world settings. The aggregate nature of the data we collected is a limitation to our study, because it prevents the analysis of relationships between change in medication use, risk factors, and changes in BP and lipid levels at an individual level. We also cannot claim causality because the study does not have a longitudinal design and we used aggregate not individual-level data. Our study is also limited by the selection of sites, which may not be representative of diabetes and CVD management in each country. The countries and clinics that we included do not adequately represent the most resource-limited settings, where findings may have been different. The goal of this study was to explore real-world experience of CVD management. It is uncertain whether any changes we see in our eight clinics are similar to those in other clinics in each country. We believe that this is the first step to understanding any change at the population level; however, we acknowledge the limitation of this study regarding its generalizability to the whole population of each country. The number of clinical services involved in this study is relatively small, and further research should be performed with population-based designs and in more locations. Adherence to treatment, as one of the likely causes of treatment failure, also needs to be addressed in future studies.

Conclusion

This study showed that from 2006 to 2015, there was improvement in the management of cholesterol, likely due to a substantial increase in statin use. The proportion of people with BP > 140/90 mmHg increased and anti-hypertensive treatment shifted from ACE inhibitors to ARBs. Such an increase in the proportion of those with BP > 140/90 mmHg occurred concomitant to the increase the in BP targets from 130/80 to 140/90 mmHg in international guidelines.

Funding sources

This study is funded by AstraZeneca.

Competing interests

This study was supported by AstraZeneca.

Acknowledgements

M.T is supported by a Monash University Postgraduate Research Scholarship and a Baker IDI Bright Sparks Scholarship, Australia. J.E.S and D.J.M are supported by National Health and Medical Research Council Senior Research Fellowships, Australia. This work is partially supported by the Victorian OHS program.

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